The authors reply

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The authors reply:

We thank Long et al (1) for their comment on our meta-analysis of randomized controlled trials (RCTs) on vitamin C supplementation in critically ill patients (2), recently published in *Critical Care Medicine*. We performed several analyses to evaluate any possible subgroup effects (e.g., different settings, route of administration, vitamin C only, high-dose IV vitamin C). We concluded that "the quality and quantity of evidence is still insufficient to draw firm conclusions, not supporting neither discouraging the systematic administration of vitamin C in these populations" (2).

Our subgroup analysis on RCTs performed in ICU patients receiving IV vitamin C with a dose higher than 5,000 mg/d (Fig. 4 in [2]) showed no significant reduction in mortality in this high-dose regimen (risk ratio, 0.83; 95% CI, 0.44–1.56; $p = 0.57$) even if the subanalysis was clearly unpowered since it included four trials and 289 patients, and further limited by clinical heterogeneity (subsetting, daily dose, year of publication). The results of secondary outcomes were inconclusive too (2).

As suggested by Long et al (1), we have now performed a subgroup analysis on mortality in ICU patients receiving IV vitamin C with a dose higher than 2,000 mg/d (six trials and 513 patients) and the results are similar (risk ratio, 0.89; 95% CI, 0.59–1.34; $p = 0.56$) (**Fig. 1**).

The pharmacological and pathophysiological rationale behind vitamin C administration in critically ill patients is strong and even a stronger rationale supports a high-dose IV regimen. This interesting rationale is nicely summarized by Long et al (1), but actually not supported by strong randomized evidence. On the other hand, several small RCTs supported the use of "lower dose" vitamin C regimen in a different setting (cardiac surgery). This made also low dose supplementation an interesting regimen to assess in a systematic review.

We fully agree with Long et al (1) that pharmacokinetics properties, together with pharmacodynamics and pathophysiological characteristics, must be taken into considerations when performing clinical trials. However, we should also take into consideration that some idea based on pathophysiology and pharmacology could be inconclusive or even detrimental. There are several examples in the field of critical care medicine: activated protein C in sepsis (3), levosimendan in sepsis (4), early parenteral nutrition in critically ill patients (5), polymyxin B hemoperfusion in sepsis (6), glutamine in critically ill patients (7), corticosteroids or 4% albumin in traumatic brain injury (8), aprotinin in cardiac surgery (8), and so on.

In conclusion, we found that the quality and quantity of randomized evidence is still insufficient to draw firm conclusions on effect of vitamin C on clinically relevant outcomes. In cardiac surgery, beneficial effects on postoperative atrial fibrillation and ICU or hospital length of stay are unclear. In ICU patients, aggregated randomized evidence does not support neither discourage the administration of vitamin C in order to reduce mortality. High-dose IV vitamin C is a fascinating option that merits further investigation.

The authors have disclosed that they do not have any potential conflicts of interest.

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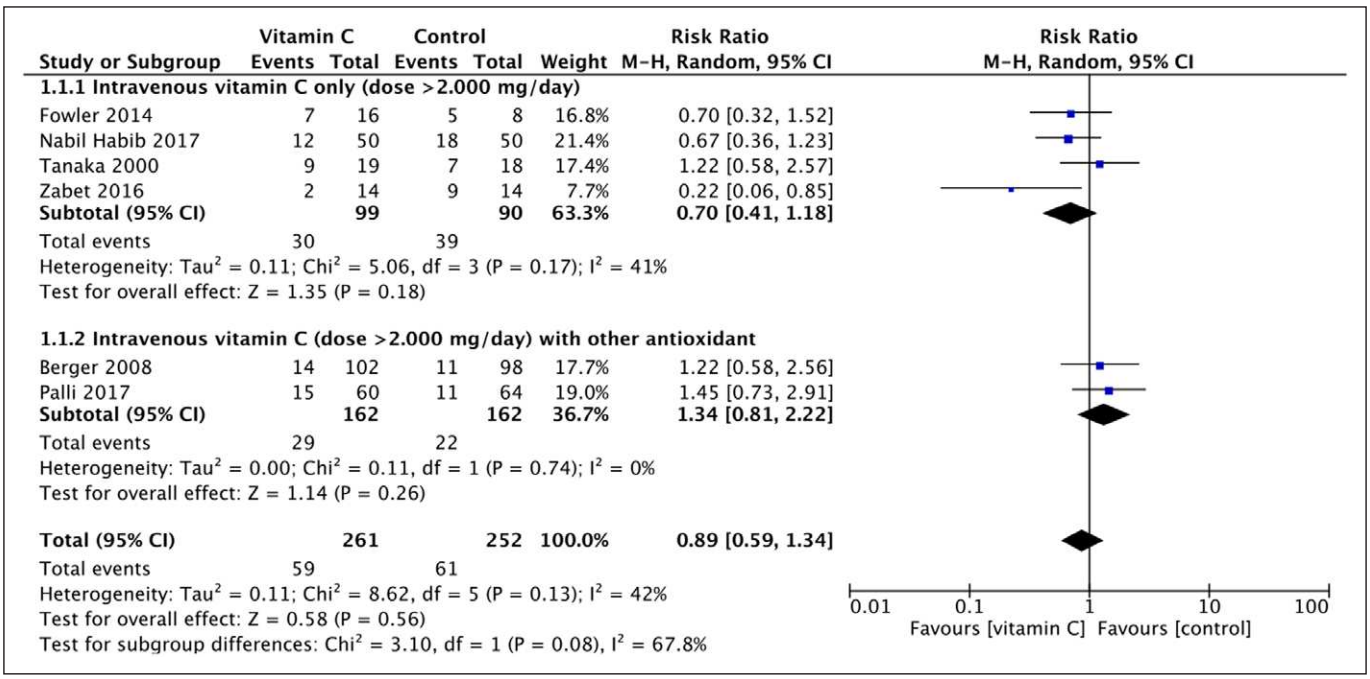

Figure 1. Forest plot for mortality at longest follow-up available in ICU patients randomized to receive high-dose IV vitamin C. *df* = degrees of freedom, M-H = Mantel-Haenszel.

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REFERENCES

1. Long MT, Hess AS, Ries MP, et al: Dosing Matters! Vitamin C in Critical Illness. *Crit Care Med* 2019; 47:e1042
2. Putzu A, Daems AM, Lopez-Delgado JC, et al: The effect of vitamin C on clinical outcome in critically ill patients: A systematic review with meta-analysis of randomized controlled trials. *Crit Care Med* 2019; 47:774–783
3. Ranieri VM, Thompson BT, Barie PS, et al; PROWESS-SHOCK Study Group: Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med* 2012; 366:2055–2064
4. Gordon AC, Perkins GD, Singer M, et al: Levosimendan for the prevention of acute organ dysfunction in sepsis. *N Engl J Med* 2016; 375:1638–1648
5. Casaer MP, Mesotten D, Hermans G, et al: Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011; 365:506–517
6. Dellinger RP, Bagshaw SM, Antonelli M, et al; EUPHRATES Trial Investigators: Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: The EUPHRATES randomized clinical trial. *JAMA* 2018; 320:1455–1463
7. Cook D, Jones G, Albert M, et al: A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med* 2013; 368:1489–1497
8. Sartini C, Lomivorotov V, Pisano A, et al: A systematic review and international web-based survey of randomized controlled trials in the perioperative and critical care setting: Interventions increasing mortality. *J Cardiothorac Vasc Anesth* 2019; 33:2685–2694

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